

# Integrated care to improve outcomes for adults with advanced HIV disease

<b>Submission date</b> 02/11/2021	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 05/11/2021	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 16/07/2024	<b>Condition category</b> Infections and Infestations	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Tuberculosis (TB) remains the most common cause of death in people living with HIV. One-quarter of the world's population are estimated to have TB infection which without tuberculosis preventative treatment may progress to cause TB disease. There is strong evidence that TB preventative treatment – as recommended for all people living with HIV by the World Health Organisation (WHO) – prevents TB infection from progressing to TB disease. This study aims to investigate the best strategy for providing tuberculosis preventative treatment for the prevention of TB disease for people living with HIV and cryptococcal meningitis.

### Who can participate?

Patients aged over 18 years who have both HIV infection and cryptococcal meningitis

### What does the study involve?

Participants will all be given a short course of tuberculosis preventative treatment consisting of 1 month of isoniazid and rifapentine. They will be randomly allocated to start treatment either as an inpatient or as an outpatient. Participants will be followed up until week 18 to determine treatment completion, safety and effectiveness.

### What are the possible benefits and risks of participating?

By taking tuberculosis preventative treatment it is anticipated that participants will have a reduced chance of developing TB disease or dying from TB. Participants will be cared for by the specialist meningitis research team. There is the possibility of side effects from the anti-tuberculous drugs used in the study. Rifapentine and isoniazid are both usually safe and well-tolerated but side effects have been reported. Most patients taking rifapentine will notice that their urine, tears, sweat and sputum turns red. This is temporary side effect and the colour will return to normal once a participant stops taking the rifapentine. Some patients report feeling generally unwell when taking rifapentine with flu-like symptoms or nausea, loss of appetite but these symptoms are again temporary and not generally harmful. Serious complications associated can occur and include liver problems, kidney problems, hypersensitivity reactions, or abnormalities with blood cells. These complications are rare. Participants will be given ample education about possible reactions. Participants will be reviewed regularly by the specialist research team and will have regular safety monitoring blood tests.

Where is the study run from?

1. London School of Hygiene & Tropical Medicine (LSHTM) (UK)
2. Infectious Diseases Institute (Uganda)

When is the study starting and how long is it expected to run for?

June 2021 to November 2024

Who is funding the study?

Wellcome Trust as part of the Wellcome Global Health Research Clinical PhD Fellowship programme (LSHTM) (UK)

Who is the main contact?

Dr Jayne Ellis

[jayne.ellis1@lshtm.ac.uk](mailto:jayne.ellis1@lshtm.ac.uk)

## Contact information

### Type(s)

Scientific

### Contact name

Dr Jayne Ellis

### ORCID ID

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### Contact details

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## Additional identifiers

### EudraCT/CTIS number

Nil known

### IRAS number

### ClinicalTrials.gov number

Nil known

### Secondary identifying numbers

V2.5, 222938/Z/21/Z

## Study information

**Scientific Title**

Integrated management of cryptococcal and opportunistic infections to improve outcomes in advanced HIV disease: a strategy trial

**Acronym**

IMPROVE

**Study objectives**

Research question: What is the preferred strategy (safety and feasibility) for delivery of 1HP (1 month of isoniazid and rifapentine) TB preventive therapy (TPT) for adults with HIV-associated cryptococcal meningitis?

Study hypothesis: Early (inpatient initiation) 1HP TPT will be non-inferior to standard (outpatient initiation) 1HP TPT with respect to TB-disease free 1HP treatment completion in individuals in whom active TB has been excluded, and 1HP TPT is feasible (adherence and tolerability) and safe (adverse events) in patients with HIV-associated cryptococcal meningitis.

**Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

1. Approved 05/08/2021, Mulago Research and Ethics Committee (PO Box 7051, Kampala, Uganda; +256 (0) 41554008/1; mulagohospitalrec@gmail.com), ref: MHREC 2021-25
2. Approved 07/06/2021, London School of Hygiene & Tropical Medicine Observational / Interventions Research Ethics Committee (Room LG36, Keppel Street, London, WC1E 7HT, UK; +44 (0)20 7927 2221; ethics@lshtm.ac.uk), ref: 24059

**Study design**

Nested randomized strategy trial

**Primary study design**

Interventional

**Secondary study design**

Randomised controlled trial

**Study setting(s)**

Hospital

**Study type(s)**

Prevention

**Participant information sheet**

See additional files

**Health condition(s) or problem(s) studied**

HIV-associated cryptococcal meningitis

**Interventions**

A nested randomised strategy trial to evaluate the safety and feasibility of two strategies for the delivery of TB preventive therapy (TPT) in HIV-associated cryptococcal meningitis: inpatient

initiation (early, week 2) or outpatient initiation (standard, week 6) delivery of 1HP (1 month of isoniazid and rifapentine) TPT.

Participants will be randomised individually, using random block size, using a computer-generated programme. Randomisation will be stratified by study sites only. Participants will be randomised to receive either a 1-month course of rifapentine 600 mg daily plus isoniazid 300 mg daily (1HP) to be initiated as an inpatient or as an outpatient. Amongst participants in the inpatient initiation arm, 1HP TPT will be started in hospital during the second week after cryptococcal meningitis diagnosis. Amongst participants in the outpatient initiation arm, 1HP TPT will be started in the outpatient clinic during the sixth week after cryptococcal meningitis diagnosis.

## **Intervention Type**

Drug

## **Phase**

Phase II/III

## **Drug/device/biological/vaccine name(s)**

Rifapentine, isoniazid

## **Primary outcome measure**

TB-disease free 1HP treatment completion at 18 weeks (after cryptococcal meningitis diagnosis and commencement of anti-fungal therapy). Treatment completion is defined as participant-reported adherence to >90% of the study medications for the duration of the trial. TB disease-free at 18 weeks is defined as (1) not receiving a diagnosis of active TB disease for the duration of the trial and (2) a negative WHO TB symptom screen at trial completion.

## **Secondary outcome measures**

1. 1HP treatment completion (defined as participant-reported adherence to >90% of the study medications) at 18 weeks
2. 1HP discontinuation of the study drugs for  $\geq 5$  consecutive days for any reason, measured using participant interviews and pill counts at 18 weeks
3. Incidence of grade 3-4 adverse events and serious adverse events (SAEs), measured using clinical and laboratory review at 18 weeks
4. Incidence of drug-induced liver injury defined as elevation of blood transaminase (ALT) alone  $\geq 5 \times$  ULN (or ALT  $\geq 3 \times$  ULN if bilirubin abnormal) or alkaline phosphatase (ALP) alone  $\geq 2 \times$  ULN, measured at 18 weeks
5. Incident active TB (defined as clinician diagnosed TB based upon clinical syndrome and/or radiological evidence and/or mycobacteriological evidence), measured at 18 weeks
6. Survival measured using clinical review at 18 weeks
7. Fluconazole, rifapentine and dolutegravir concentrations measured using liquid chromatography-tandem mass spectrometry on days 5 and 14 of 1HP (for n=20 participants)

## **Overall study start date**

07/06/2021

## **Completion date**

25/11/2024

## **Eligibility**

**Key inclusion criteria**

HIV-positive adults (aged  $\geq 18$  years) with HIV-associated cryptococcal meningitis (CSF CrAg positive)

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

205

**Key exclusion criteria**

1. Active TB disease (as evidenced by any positive TB screening test or taking TB therapy at time of screening)
2. Jaundice
3. Abnormal liver function tests (bilirubin  $>3.5$  mg/dl or ALT  $>200$  IU/L)
4. Active hepatitis B infection (defined as hepatitis B surface antigen positive)
5. Known chronic liver disease
6. A clinical syndrome which in the opinion of the attending clinician, puts the patient at significant risk if he/she were to participate in the 1HP trial
7. Pregnant
8. Breastfeeding
9. Hypersensitivity to rifamycins or isoniazid
10. Contraindicated medication(s) (e.g. protease inhibitor)

**Date of first enrolment**

25/11/2021

**Date of final enrolment**

25/11/2023

**Locations****Countries of recruitment**

Uganda

**Study participating centre**

**Kiruddu National Referral Hospital**

Kampala

Uganda

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## Sponsor information

### Organisation

London School of Hygiene & Tropical Medicine

### Sponsor details

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England

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### Sponsor type

University/education

### Website

<http://www.lshtm.ac.uk/>

### ROR

<https://ror.org/00a0jsq62>

## Funder(s)

### Funder type

Research organisation

### Funder Name

Wellcome Trust

### Alternative Name(s)

Wellcome, WT

### Funding Body Type

Private sector organisation

### Funding Body Subtype

Trusts, charities, foundations (both public and private)

**Location**  
United Kingdom

## Results and Publications

**Publication and dissemination plan**

The researchers will share results through presentations at scientific conferences and in peer-reviewed open-access journals.

**Intention to publish date**

06/06/2025

**Individual participant data (IPD) sharing plan**

The anonymised database will be shared with the journal, if required, upon request from Dr Jayne Ellis (jayne.ellis1@lshtm.ac.uk).

**IPD sharing plan summary**

Available on request

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Participant information sheet</a>	version 5	23/07/2021	05/11/2021	No	Yes
<a href="#">Participant information sheet</a>	Luganda version 5	23/07/2021	05/11/2021	No	Yes
<a href="#">Protocol file</a>	version 2.5	19/10/2021	05/11/2021	No	No
<a href="#">Protocol article</a>		05/06/2024	16/07/2024	Yes	No